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(54) Acid preparation by de-protection

(57) An acid compound (or salt thereof) comprising at least two nitrogen groups and at least one carboxylic acid group (or salt thereof) is prepared from a nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a protecting group by removing the protecting group from the carboxylic acid group of the nitrogen compound. The product is e.g. ethylenediaminedisuccinic acid.

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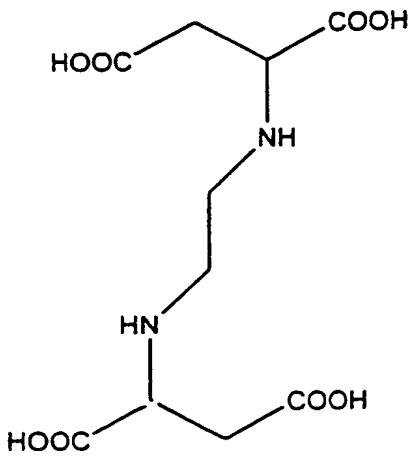
Figure 1



S,S-EDDS

Figure 2

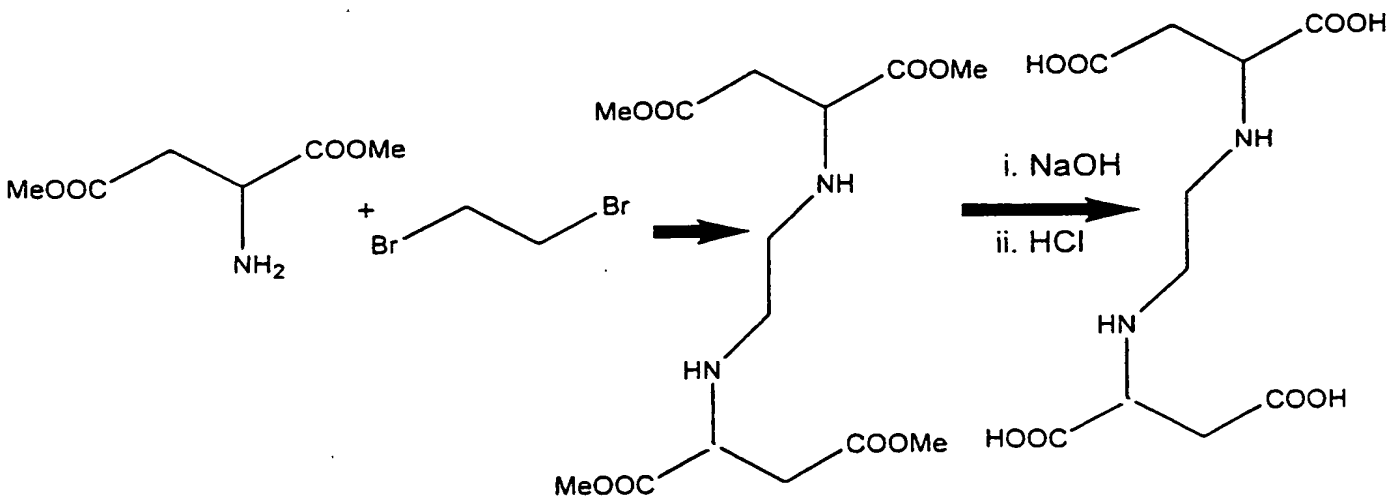
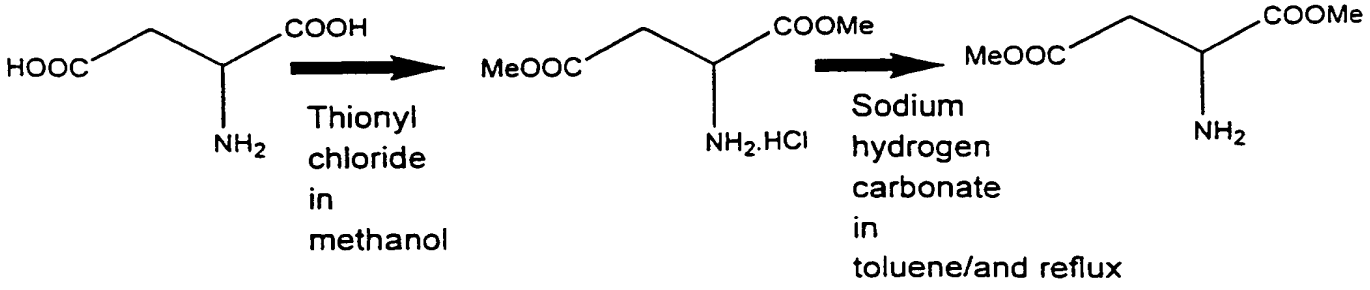


Figure 3



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PROCESS

The present invention relates to a process for preparing amine compounds.

In particular, the present invention relates to a process for preparing alkylated amino acids. More in particular, the present invention relates to a process for the preparation of N-alkylated amino acids and, optionally, esters or salts thereof. Especially the process is for preparing (S,S)-ethylenediaminedisuccinic acid or an ester or a salt thereof.

Certain compounds having amino acid moieties linked by a group joining their nitrogen atoms have a variety of uses mainly based on their metal chelating properties. Typical examples include their use as corrosion inhibitors, and in detergents, photographic developing solutions, rubber and resin formulations and metal treatments. One particular example is ethylenediaminedisuccinic acid ("EDDS") which has two chiral centres. The S,S-enantiomer of EDDS is preferred because of its biodegradability and its better chelating properties. (S,S)-EDDS is shown in Figure 1.

Racemic EDDS is usually prepared by the reaction of maleic anhydride with ethylenediamine in NaOH solution, according to the procedure by W.M. Ramsey and C. Kerzerian of the Stauffer Chemical Company, US 3,158,635. (S,S)-EDDS can be manufactured by a variety of different routes. A typical route is the reaction of NaOH with L-aspartic acid and dibromoethane following the protocol of Neal, J.A. and Rose, N.J. (Inorganic Chemistry, Vol. 7, No. 11, November 1968, pages 2405-2412, particularly page 2406). However, even though this synthetic route is the one that is typically used it is usually difficult to obtain economic yields of (S,S)-EDDS. Furthermore it is difficult to obtain highly pure (S,S)-EDDS.

The present invention seeks to overcome the problems associated with the known processes.

In this regard, the present invention seeks to provide a process that can be used to prepare amine compounds, especially secondary amine compounds, economically and/or in good yields.

In particular, the present invention seeks to provide a process that enables compounds like EDDS, more especially (S,S)-EDDS, to be prepared in high yields, economic yields and/or high purity.

According to the present invention there is provided a process for preparing an acid compound (or salt thereof) comprising at least two nitrogen groups and at least one carboxylic acid group (or salt thereof) from a first nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a first protecting group, the process comprising a first de-protection step of removing the first protecting group from the carboxylic acid group of the first nitrogen compound thereby to form the acid compound (or salt thereof).

There are a number of advantages associated with the present invention. For example, it enables compounds like EDDS, more especially (S,S)-EDDS, to be prepared in high yields. It also enables compounds like EDDS, more especially (S,S)-EDDS, to be prepared in economic yields. It also enables compounds like EDDS, more especially (S,S)-EDDS, to be prepared at a high purity. The present invention also provides a reliable process for preparing optically active compounds, such as (S,S)-EDDS, by use of a substantially aqueous reaction medium/media.

A key advantage of the present invention is that the degree of alkylation of the amine can be controlled.

In this regard, in the final product, the acid compound can be substantially only mono-alkylated.

Preferably, the nitrogen groups are linked by a hydrocarbyl group or a substituted hydrocarbyl group, which may be linear or branched and which may comprise another functional group or other functional groups.

Preferably, the acid compound comprises a plurality of carboxylic acid groups and the first nitrogen compound comprises a plurality of carboxylic acid groups each protected by a first protecting group which may be the same or different, preferably wherein the first protecting groups are the same.

Preferably, the acid compound comprises at least one chiral centre.

Preferably, the acid compound comprises at least two chiral centres, preferably two chiral centres.

Preferably, the acid compound comprises two or more carboxylic acid groups.

Preferably, the acid compound comprises at least four carboxylic acid groups, preferably four carboxylic acid groups.

Preferably, the first de-protection step is conducted using a substantially aqueous medium.

Preferably, the first de-protection step is conducted using an inorganic base or acid, preferably using an inorganic base, more preferably using aqueous NaOH.

If the de-protection step forms a salt of the acid compound then the salt form can be easily converted to the acid compound.

For example, if the de-protection step is conducted using an inorganic base, such as aqueous NaOH, and the resultant product is the salt of the acid compound then the salt can be easily converted to the acid compound by addition of an inorganic or an

organic acid, preferably HCl.

If the de-protection step forms the acid compound then the acid compound can be easily converted to the salt of the acid compound. For example, addition of an inorganic base, such as NaOH to the acid compound could form a sodium salt of the acid compound.

Preferably, the or each first protecting group is an alkyl group (i.e. the or each protected carboxylic acid is an ester).

Preferably, the or each first protecting group is a linear alkyl group.

Preferably, the or each first protecting group is a methyl group.

Preferably, the acid compound is EDDS.

Preferably, the acid compound is (S,S)-EDDS.

Preferably, the first nitrogen compound is prepared by reacting at least a second nitrogen compound and a third nitrogen compound with an organo halo compound, wherein the second nitrogen compound and the third nitrogen compound independently comprise at least one primary amine group and wherein the second nitrogen compound and/or the third nitrogen compound comprise at least one protected carboxylic acid group.

Preferably, the first nitrogen compound is prepared by reacting at least a second nitrogen compound and a third nitrogen compound with an organo halo compound, wherein the second nitrogen compound and the third nitrogen compound independently comprise at least one primary amine group and at least one protected carboxylic acid group.

Preferably, the second nitrogen compound and/or the third nitrogen compound comprise a plurality of protected carboxylic acid groups.

Preferably, the or each carboxylic acid is protected by an alkyl group (i.e. the or each protected carboxylic acid is an ester).

Preferably, the alkyl group is a linear alkyl group.

Preferably, the alkyl group is a methyl group.

Preferably, the organo halo compound is of the formula X-A-Y, wherein X and Y independently are halo atoms which may be the same or different, and wherein A is a hydrocarbyl group or a substituted hydrocarbyl group, which may be linear or branched and which may comprise another functional group or other functional groups, and in which X and Y are attached to aliphatic or cycloaliphatic carbon atoms.

Preferably, A is of the general formula $(CH_2)_n$ where n is 1 or 20, optionally substituted with groups which are unreactive under the reaction conditions.

Preferably, A is $(CH_2)_n$ or cycloalkyl.

Preferably, A is $(CH_2)_n$ where n is 2, 3 or 4 or 1,2- or 1,4-cyclohexyl.

Preferably, A is $(CH_2)_2$.

Preferably, X and/or Y is Br.

Preferably, X and Y are the same.

Preferably, the second nitrogen compound and/or the third nitrogen compound comprise at least one chiral centre, preferably one chiral centre.

Preferably, the second nitrogen compound and the third nitrogen compound are the same.

Preferably, the second nitrogen compound and/or the third nitrogen compound are respectively prepared from a fourth nitrogen compound and a fifth nitrogen compound wherein the fourth nitrogen compound comprises at least one primary amine group protected with a second protecting group and at least one protected carboxylic acid group, and wherein the fifth nitrogen compound comprises at least one primary amine group protected with a third protecting group and at least one protected carboxylic acid group, the process comprising a second de-protection step of removing the second protecting group from the protected primary amine group of the fourth nitrogen compound and a third de-protection step of removing the third protecting group from the protected primary amine group of the fifth nitrogen compound to form respectively the second nitrogen compound and the third nitrogen compound.

Preferably, the fourth nitrogen compound and/or the fifth nitrogen compound comprise a plurality of protected carboxylic acid groups.

Preferably, the or each carboxylic acid is protected by an alkyl group (i.e. the or each protected carboxylic acid is an ester).

Preferably, the alkyl group is a linear alkyl group.

Preferably, the alkyl group is a methyl group.

Preferably, the fourth nitrogen compound and/or the fifth nitrogen compound comprise at least one chiral centre, preferably one chiral centre.

Preferably, the fourth nitrogen compound and the fifth nitrogen compound are the same.

Preferably, the second protecting group and the third protecting group are the same.

Preferably, the second protecting group and/or the third protecting group is an acid salt.

Preferably, the acid salt is an HCl salt.

Preferably, the second de-protection step and/or the third deprotection step is conducted using an organic medium, preferably toluene.

Preferably, the second de-protection step and/or the third deprotection step is conducted using an inorganic base, preferably sodium hydrogen carbonate.

Preferably, the second de-protection step is the same as the third deprotection step.

Preferably, wherein the second de-protection step is conducted at the same time as the third deprotection step.

Preferably, the fourth nitrogen compound and/or the fifth nitrogen compound are respectively prepared from a sixth nitrogen compound and a seventh nitrogen compound wherein the sixth nitrogen compound comprises at least one primary amine group and at least one carboxylic acid group and wherein the seventh nitrogen compound comprises at least one primary amine group and at least one carboxylic acid group, the process comprising protecting (independently or together) the primary amine group and the carboxylic acid group of each of the sixth nitrogen compound and the seventh nitrogen compound.

Preferably, the primary amine group and the carboxylic acid are protected at the same time.

Preferably, the protection step includes the formation of an ester.

Preferably, the protection step is conducted in an organic medium, preferably methanol.

Preferably, the protection step includes the use of thionyl chloride or gaseous HCl.

Preferably, the sixth nitrogen compound and/or the seventh nitrogen compound comprise at least one chiral centre, preferably one chiral centre.

Preferably, the sixth nitrogen compound and the seventh nitrogen compound are the same.

Preferably, the sixth nitrogen compound and/or the seventh nitrogen compound are/is an amino acid.

Preferably, the amino acid is an acidic amino acid.

Preferably, the amino acid is aspartic acid.

Preferably, the amino acid is L-amino acid.

Preferably, the amino acid is L-aspartic acid.

A further advantage of the present invention is that it provides a process that can allow *in situ* production of the acid compound (or salt thereof) and/or any one of the first, second, third, fourth or fifth nitrogen compounds without requiring the need to isolate any intermediates in the reaction process.

In some cases the intermediate or intermediates could be isolated, but in some instances (such as with use of organic reation media to prepare the first nitrogen compound and subsequent conversion to the acid compound using at least NaOH) preferably the intermediate or intermediates is/are not isolated.

For the process of the present invention, the nitrogen compounds can comprise any one or more of a substituted alkyl group (preferably C_{1-20}, more preferably C_{1-12}), an unsubstituted alkyl group (preferably C_{1-20}, more preferably C_{1-12}), a saturated alkyl group (preferably C_{1-20}, more preferably C_{1-12}), an unsaturated alkyl group (preferably C_{1-20}, more preferably C_{1-12}), an unsubstituted aryl group (preferably C_{1-20}, more preferably C_{1-12}) or a substituted aryl group (preferably C_{1-20}, more preferably C_{1-12}), including combinations thereof.

Typical amino acids for use in the process of the present invention include any one or more of the 26 or so naturally occurring amino acids listed in standard textbooks, including the derivatives thereof.

The amino acid may be any one or more of a "neutral" amino acid, a "basic" amino acid or an "acidic" amino acid.

However, preferably the amino acid for use in the process of the present invention is not cysteine. This is because this amino acid has an -SH group which could undergo unwanted side reactions.

In the process of the present invention an amino acid having an α-amino group (e.g. aspartic acid) can be reacted. Alternatively, or in addition, in the process of the present invention an amino acid having a β-amino group (e.g. β-alanine) can be reacted.

Examples of neutral amino acids that may be used in the present invention include glycine, alanine, valine, leucine, norleucine, phenylalanine, tyrosine, serine, cystine, threonine, methionine, di-iodotyrosine, thyroxine, dibromotyrosine, tryptophan, proline and hydroxyproline.

Examples of basic amino acids that may be used in the present invention include ornithine, arginine, lysine and histidine.

Examples of acidic amino acids that may be used in the process of the present invention include aspartic acid, glutamic acid and β-hydroxyglutamic acid.

The preferred amino acids for the process of the present invention are those with two carboxyl groups and one amino group - i.e. the acidic amino acids listed above. Aspartic acid and glutamic acid are the most preferred of the three.

Specific optical isomers, particularly the L-form, are desirable because they increase biodegradability and in some cases, may also improve the chelating effect. Alternatively, other amino acids may be reacted in the process of the present invention, such as D- or DL- amino acids, for example D-aspartic acid or DL-aspartic acid, to generate corresponding R,R- or racemic products having at least two nitrogen groups, such as R,R- or racemic EDDS.

For the process of the present invention, preferably the unreacted nitrogen compounds are recovered and then recycled into the process.

For the process of the present invention, the organo-halo compound can comprise any one or more of a substituted alkyl group (preferably C_{1-20}, more preferably C_{1-12}), an unsubstituted alkyl group (preferably C_{1-20}, more preferably C_{1-12}), a saturated alkyl group (preferably C_{1-20}, more preferably C_{1-12}), an unsaturated alkyl group (preferably C_{1-20}, more preferably C_{1-12}), an unsubstituted aryl group (preferably C_{1-20}, more preferably C_{1-12}) or a substituted aryl group (preferably C_{1-20}, more preferably C_{1-12}),

including combinations thereof. The organo-halo compound can comprise more than one saturated alkyl halo group. If more than one organo-halo compound or group is reacted the organo-halo compounds or groups can be the same or different. The substituted alkyl or aryl groups can be alkyl or aryl groups with one or more functional groups.

Preferably the organo-halo compound is of the formula X-A where X is a halo atom and A is a hydrocarbyl group or a substituted hydrocarbyl group which may be linear or branched and which may comprise another functional group or other functional groups, and in which X is attached to aliphatic or cycloaliphatic carbon atoms (preferably C_{1-20}, more preferably C_{1-12}).

In a preferred embodiment, the organo-halo compound can be of the formula X-A-Y where X and Y are halo atoms which may be the same or different and A is a hydrocarbyl group or a substituted hydrocarbyl group which may be linear or branched and which may comprise another functional group or other functional groups, and in which X and Y are attached to aliphatic or cycloaliphatic carbon atoms (preferably C_{1-20}, more preferably C_{1-12}). The substituted alkyl or aryl groups can be alkyl or aryl groups with one or more functional groups.

Preferably, the organo-halo compound is an organo bromo compound, more preferably dibromoethane. Alternatively, the organo-halo compound can be dichloroethane.

In the process of the present invention the nitrogen compounds can comprise more than one additional functional groups, even further nitrogen groups, which need not be reactive.

Likewise, in the process of the present invention the organo halo compound can comprise functional groups, which need not be reactive.

Also, in the process of the present invention an additional nitrogen compound or additional nitrogen compounds may be reacted.

Likewise, in the process of the present invention an additional organo halo compound or additional organo halo compounds may be reacted, which organo halo compound or organo halo compounds can independently comprise one or more halo groups or other functional groups.

In the process of the present invention, a mixture of nitrogen compounds and/or organo halo compounds can be reacted. Other reactive compounds may be present in the reaction medium.

The process of the present invention can be conducted at any appropriate pH condition. Preferably, the first de-protection step is conducted at a pH in the range of 7-14, more preferably in the range of 9-14 and even more preferably in the range 11-14. The pH may be maintained with alkali (i.e. a base), typically aq. NaOH solution, though a wide variety of water-soluble inorganic and organic bases may be used. In some instances, it will be desirable to add alkali during the reaction.

The reaction medium for the first deprotecting step is normally wholly aqueous but the presence of other solvents such as ethanol is not excluded.

If the acid compound is less soluble than the starting reactant(s) then the reaction mixture can be diluted to a level at which remaining starting reactant or reactants is(are) soluble, followed by acidification and selective crystallisation of the desired product.

The acid compound may be prepared in salt form by the process of the present invention.

The process of the present invention can be carried out under pressure. If so, preferably the pressure is at least 1 bar gauge.

For the process of the present invention, preferably the acid compound is recovered from the reaction mixture.

In summation the present invention provides a process for preparing an acid compound (or salt thereof) which comprises at least two nitrogen groups and at least one carboxylic acid group (or salt thereof), such as EDDS more especially (S,S)-EDDS. The process comprises forming the acid compound from a first nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a first protecting group, wherein the process includes a first de-protection step of removing the first protecting group from the carboxylic acid group of the first nitrogen compound thereby to form the acid compound (or salt thereof). The acid compound can be easily converted to the salt form of the acid compound and *vice versa*.

A preferred embodiment of the present invention relates to a process for preparing an acid compound (or salt thereof) comprising at least two nitrogen groups and at least one carboxylic acid group (or salt thereof) (preferably EDDS, more preferably (S,S)-EDDS) from a first nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a first protecting group, the process comprising a first de-protection step of removing the first protecting group from the carboxylic acid group of the first nitrogen compound thereby to form the acid compound (or salt thereof), wherein the first nitrogen compound is prepared by reacting at least a second nitrogen compound and a third nitrogen compound with an organo halo compound, wherein the second nitrogen compound and the third nitrogen compound independently comprise at least one primary amine group and wherein the second nitrogen compound and/or the third nitrogen compound comprise at least one protected carboxylic acid group, preferably wherein the organo halo compound is of the formula X-A-Y, wherein X and Y independently are halo atoms which may be the

same or different, and wherein A is a hydrocarbyl group or a substituted hydrocarbyl group which may be linear or branched and which may comprise another functional group or other functional groups, and in which X and Y are attached to aliphatic or cycloaliphatic carbon atoms.

A more preferred embodiment of the present invention relates to a process for preparing an acid compound (or salt thereof) comprising at least two nitrogen groups and at least one carboxylic acid group (or salt thereof) (preferably EDDS, more preferably (S,S)-EDDS) from a first nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a first protecting group, the process comprising a first de-protection step of removing the first protecting group from the carboxylic acid group of the first nitrogen compound thereby to form the acid compound (or salt thereof), wherein the first nitrogen compound is prepared by reacting at least a second nitrogen compound and a third nitrogen compound with an organo halo compound, wherein the second nitrogen compound and the third nitrogen compound independently comprise at least one primary amine group and wherein the second nitrogen compound and/or the third nitrogen compound comprise at least one protected carboxylic acid group, further wherein the second nitrogen compound and the third nitrogen compound are respectively prepared from a fourth nitrogen compound and a fifth nitrogen compound wherein the fourth nitrogen compound comprises at least one primary amine group protected with a second protecting group and at least one protected carboxylic acid group, and wherein the fifth nitrogen compound comprises at least one primary amine group protected with a third protecting group and at least one protected carboxylic acid group, the process comprising a second de-protection step of removing the second protecting group from the protected primary amine group of the fourth nitrogen compound and a third de-protection step of removing the third protecting group from the protected primary amine group of the fifth nitrogen compound to form respectively the second nitrogen compound and the third nitrogen compound, preferably wherein the organo halo compound is of the formula X-A-Y, wherein X and Y independently are halo atoms which may be the same or different, and wherein

A is a hydrocarbyl group or a substituted hydrocarbyl group which may be linear or branched and which may comprise another functional group or other functional groups, and in which X and Y are attached to aliphatic or cycloaliphatic carbon atoms.

An even more preferred embodiment of the present invention relates to a process for preparing an acid compound (or salt thereof) comprising at least two nitrogen groups and at least one carboxylic acid group (or salt thereof) (preferably EDDS, more preferably (S,S)-EDDS) from a first nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a first protecting group, the process comprising a first de-protection step of removing the first protecting group from the carboxylic acid group of the first nitrogen compound thereby to form the acid compound (or salt thereof), wherein the first nitrogen compound is prepared by reacting at least a second nitrogen compound and a third nitrogen compound with an organo halo compound, wherein the second nitrogen compound and the third nitrogen compound independently comprise at least one primary amine group and wherein the second nitrogen compound and/or the third nitrogen compound comprise at least one protected carboxylic acid group, further wherein the second nitrogen compound and the third nitrogen compound are respectively prepared from a fourth nitrogen compound and a fifth nitrogen compound wherein the fourth nitrogen compound comprises at least one primary amine group protected with a second protecting group and at least one protected carboxylic acid group, and wherein the fifth nitrogen compound comprises at least one primary amine group protected with a third protecting group and at least one protected carboxylic acid group, the process comprising a second de-protection step of removing the second protecting group from the protected primary amine group of the fourth nitrogen compound and a third de-protection step of removing the third protecting group from the protected primary amine group of the fifth nitrogen compound to form respectively the second nitrogen compound and the third nitrogen compound, further wherein the fourth nitrogen compound and the fifth nitrogen compound are respectively prepared from a sixth nitrogen compound and a seventh nitrogen

compound wherein the sixth nitrogen compound comprises at least one primary amine group and at least one carboxylic acid group and wherein the seventh nitrogen compound comprises at least one primary amine group and at least one carboxylic acid group, the process comprising protecting (independently or together) the primary amine group and the carboxylic acid group of each of the sixth nitrogen compound and the seventh nitrogen compound, preferably wherein the organo halo compound is of the formula X-A-Y, wherein X and Y independently are halo atoms which may be the same or different, and wherein A is a hydrocarbyl group or a substituted hydrocarbyl group which may be linear or branched and which may comprise another functional group or other functional groups, and in which X and Y are attached to aliphatic or cycloaliphatic carbon atoms.

Preferably any one or more of the first nitrogen compound, second nitrogen compound, third nitrogen compound, fourth nitrogen compound, fifth nitrogen compound, sixth nitrogen compound and seventh nitrogen compound is prepared under anhydrous conditions.

In a preferred embodiment of the present invention at least the first nitrogen compound is prepared under anhydrous conditions.

Preferably at least the first nitrogen compound, second nitrogen compound and third nitrogen compound are prepared under anhydrous conditions.

In a highly preferred embodiment of the present invention at least the first nitrogen compound, second nitrogen compound, third nitrogen compound, fourth nitrogen compound and fifth nitrogen compound are prepared under anhydrous conditions.

Some of the key advantages using anhydrous reaction conditions, especially for the preparation of the first nitrogen compound, include: the ability to control the degree of alkylation; and minimal loss of the reactants, such as the preferred alkylating agent DBE, due to hydrolysis.

The present invention will now be described only by way of example, in which reference shall be made to the following Figures:

Figure 1 is a representation of EDDS;

Figures 2 and 3 are schematic representations of the preparation of EDDS by a highly preferred process according to the present invention.

EXAMPLE 1

This example concerns the preparation α,β-dimethyl aspartate.

Following the methods of H Schwarz, F M Bumpus and I H Page (J Am Chem Soc, 1957, 79, 5697-5703) and P Gmeiner, P L Feldman, M Y Chu-Moyer and H Rapoport (J Org Chem, 1990, 55, 3068-3074), L-aspartic acid was converted to the dimethyl ester using thionyl chloride in methanol. This reaction is shown as the first reaction step of the reaction scheme shown in Figure 3.

Deprotection of the amine hydrochloride salt was then achieved by the action of sodium hydrogen carbonate in toluene under reflux. This reaction is shown as the second reaction step of the reaction scheme shown in Figure 3.

EXAMPLE 2

This example concerns the mono-N-alkylation of α,β-dimethyl aspartate to form tetramethyl-(S,S)-EDDS.

Adapting the method of P L Feldman and H Rapoport (J Org Chem, 1986, 51, 3882), α,β-dimethyl aspartate (8.14g, 50.5 mmoles) was placed in a reaction flask, followed by 1,2-dibromoethane (13.95g, 74.3 mmoles), sodium hydrogen carbonate (12.87g, 0.153 moles) and acetonitrile (60ml).

The resulting reaction mixture was heated (80°C) under nitrogen for 7 hours. This reaction is shown as the first reaction step of the reaction scheme shown in Figure 2.

GCMS of the reaction mixture indicated that tetramethyl ethylenediamine disuccinate had been obtained. The data are shown in the Table below.

Exp. No.	Solvent	DBE (mol.eq.)	Base (mol.eq.)	Time	Result (area %) DMA:TMEDDS:Imp
1	Hexane	1.5	3	6 hours	14 : 80 : 6
2	Acetonitrile	1.5	3	3 hours	9 : 79 : 12
3	Acetonitrile	1.5	3	6 hours	5 : 65 : 30
4	Methanol	0.5	-	24 hours	19 : 60 : 21
5	Methanol	0.5	-	4 days	26 : 62 : 12

DMA = Dimethylaspartate (starting material)
TMEDDS = Tetramethylethylene diamine disuccinate (product)

EXAMPLE 3

This example concerns the conversion of tetramethyl-(S,S)-EDDS to (S,S)-EDDS.

The tetramethyl ethylenediamine disuccinate (i.e. tetramethyl-(S,S)-EDDS) prepared in Example 2 is treated with sodium hydroxide in water for several hours. The resultant sodium salt of S,S-ethylenediamine disuccinic acid is then converted to S,S-ethylenediamine disuccinic acid (i.e. (S,S)-EDDS) by the addition of HCl. (S,S)-EDDS is then isolated. This reaction is shown as the second reaction step of the reaction scheme shown in Figure 2.

Studies showed that $NaOH/H_2O$ could be used to prepare (S,S)-EDDS, even if the reaction mixture was held at 2°C.

Additional studies showed that use of $NaOH/MeOH/H_2O$ increased the yield of (S,S)-EDDS under reflux conditions when compared with keeping the reaction mixture at 20°C.

Further studies showed that $LiOH/H_2O$ could be used to prepare (S,S)-EDDS. Surprisingly, the yields were comparable when the reaction mixture was held at either 5°C or when the reaction mixture was under relux.

In summation, the present invention provides a novel and inventive process for preparing compounds such as EDDS, more especially (S,S)-EDDS. The process of the present invention is very different from the known reactions involving monohaloalkanes.

Other modifications of the present invention will be apparent to those skilled in the art.

For example, with regard to some of the preferred aspects of the present invention, in some instances a separate deprotection step of the hydrochloride salt may not be required as sodium hydrogen carbonate is present in the alkylation reaction (i.e. *in situ* deprotection occurs); and the reactions may also proceed without $NaHCO_3$, but refluxing with $NaHCO_3$ may then be required at the end of the reaction.

CLAIMS

1. A process for preparing an acid compound (or salt thereof) comprising at least two nitrogen groups and at least one carboxylic acid group (or salt thereof) from a first nitrogen compound comprising at least two nitrogen groups and at least one carboxylic acid group protected with a first protecting group, the process comprising a first de-protection step of removing the first protecting group from the carboxylic acid group of the first nitrogen compound thereby to form the acid compound (or salt thereof).

2. A process according to claim 1 wherein the nitrogen groups are linked by a hydrocarbyl group or a substituted hydrocarbyl group, which may be linear or branched and which may comprise another functional group or other functional groups.

3. A process according to claim 1 or claim 2 wherein the acid compound comprises a plurality of carboxylic acid groups and the first nitrogen compound comprises a plurality of carboxylic acid groups each protected by a first protecting group which may be the same or different, preferably wherein the first protecting groups are the same.

4. A process according to any one of the preceding claims wherein the acid compound comprises at least one chiral centre.

5. A process according to any one of the preceding claims wherein the acid compound comprises at least two chiral centres, preferably two chiral centres.

6. A process according to any one of the preceding claims wherein the acid compound comprises two or more carboxylic acid groups.

7. A process according to any one of the preceding claims wherein the acid compound comprises at least four carboxylic acid groups, preferably four carboxylic acid groups.

8. A process according to any one of the preceding claims wherein the first de-protection step is conducted using a substantially aqueous medium.

9. A process according to any one of the preceding claims wherein the first de-protection step is conducted using an inorganic base, preferably aqueous NaOH.

10. A process according to any one of the preceding claims wherein the or each first protecting group is an alkyl group (i.e. the or each protected carboxylic acid is an ester).

11. A process according to any one of the preceding claims wherein the or each first protecting group is a linear alkyl group.

12. A process according to any one of the preceding claims wherein the or each first protecting group is a methyl group.

13. A process according to any one of the preceding claims wherein the acid compound is EDDS.

14. A process according to any one of the preceding claims wherein the acid compound is (S,S)-EDDS.

15. A process according to any one of the preceding claims wherein the first nitrogen compound is prepared by reacting at least a second nitrogen compound and a third nitrogen compound with an organo halo compound, wherein the second nitrogen compound and the third nitrogen compound independently comprise at least one primary amine group and wherein the second nitrogen compound and/or the third

nitrogen compound comprise at least one protected carboxylic acid group.

16. A process according to claim 15 wherein the second nitrogen compound and/or the third nitrogen compound comprise a plurality of protected carboxylic acid groups.

17. A process according to claim 15 or claim 16 wherein the or each carboxylic acid is protected by an alkyl group (i.e. the or each protected carboxylic acid is an ester).

18. A process according to claim 17 wherein the alkyl group is a linear alkyl group.

19. A process according to claim 18 wherein the alkyl group is a methyl group.

20. A process according to any one of claims 15 to 19 wherein the organo halo compound is of the formula X-A-Y, wherein X and Y independently are halo atoms which may be the same or different, and wherein A is a hydrocarbyl group or a substituted hydrocarbyl group which may be linear or branched and which may comprise another functional group or other functional groups, and in which X and Y are attached to aliphatic or cycloaliphatic carbon atoms.

21. A process according to claim 20 wherein A is of the general formula $(CH_2)_n$ where n is 1 or 20, optionally substituted with groups which are unreactive under the reaction conditions.

22. A process according to claim 21 wherein A is $(CH_2)_n$ or cycloalkyl.

23. A process according to claim 22 wherein A is $(CH_2)_n$ where n is 2, 3 or 4 or 1,2- or 1,4-cyclohexyl.

24. A process according to claim 23 wherein A is $(CH_2)_2$.

25. A process according to any one of claims 20 to 24 wherein X and/or Y is Br.

26. A process according to any one of claims 20 to 25 wherein X and Y are the same.

27. A process according to any one of claims 15 to 26 wherein the second nitrogen compound and/or the third nitrogen compound comprise at least one chiral centre, preferably one chiral centre.

28. A process according to any one of claims 15 to 27 wherein the second nitrogen compound and the third nitrogen compound are the same.

29. A process according to any one of claims 15 to 28 wherein the second nitrogen compound and the third nitrogen compound are respectively prepared from a fourth nitrogen compound and a fifth nitrogen compound wherein the fourth nitrogen compound comprises at least one primary amine group protected with a second protecting group and at least one protected carboxylic acid group, and wherein the fifth nitrogen compound comprises at least one primary amine group protected with a third protecting group and at least one protected carboxylic acid group, the process comprising a second de-protection step of removing the second protecting group from the protected primary amine group of the fourth nitrogen compound and a third de-protection step of removing the third protecting group from the protected primary amine group of the fifth nitrogen compound to form respectively the second nitrogen compound and the third nitrogen compound.

30. A process according to claim 29 wherein the fourth nitrogen compound and/or the fifth nitrogen compound comprise a plurality of protected carboxylic acid groups.

31. A process according to claim 29 or claim 30 wherein the or each carboxylic acid is protected by an alkyl group (i.e. the or each protected carboxylic acid is an ester).

32. A process according to claim 31 wherein the alkyl group is a linear alkyl group.

33. A process according to claim 32 wherein the alkyl group is a methyl group.

34. A process according to any one of claims 29 to 33 wherein the fourth nitrogen compound and/or the fifth nitrogen compound comprise at least one chiral centre, preferably one chiral centre.

35. A process according to any one of claims 29 to 34 wherein the fourth nitrogen compound and the fifth nitrogen compound are the same.

36. A process according to any one of claims 29 to 35 wherein the second protecting group and the third protecting group are the same.

37. A process according to any one of claims 29 to 36 wherein the second protecting group and/or the third protecting group is an acid salt.

38. A process according to claim 37 wherein the acid is an HCl salt.

39. A process according to any one of claims 29 to 38 wherein the second deprotection step and/or the third deprotection step is conducted using an organic medium, preferably toluene.

40. A process according to any one of claims 29 to 39 wherein the second deprotection step and/or the third deprotection step is conducted using an inorganic base, preferably sodium hydrogen carbonate.

42. A process according to any one of claims 29 to 41 wherein the second deprotection step is the same as the third deprotection step.

43. A process according to any one of claims 29 to 42 wherein the second deprotection step is conducted at the same time as the third deprotection step.

44. A process according to any one of claims 29 to 43 wherein the fourth nitrogen compound and the fifth nitrogen compound are respectively prepared from a sixth nitrogen compound and a seventh nitrogen compound wherein the sixth nitrogen compound comprises at least one primary amine group and at least one carboxylic acid group and wherein the seventh nitrogen compound comprises at least one primary amine group and at least one carboxylic acid group, the process comprising protecting (independently or together) the primary amine group and the carboxylic acid group of each of the sixth nitrogen compound and the seventh nitrogen compound.

45. A process according to claim 44 wherein the primary amine group and the carboxylic acid are protected at the same time.

46. A process according to claim 44 or claim 45 wherein the protection step includes the formation of an ester.

47. A process according to any one of claims 44 to 46 wherein the protection step is conducted in an organic medium, preferably methanol.

48. A process according to any one of claims 44 to 47 wherein the protection step includes the use of thionyl chloride or gaseous HCl.

49. A process according to any one of claims 44 to 48 wherein the sixth nitrogen compound and/or the seventh nitrogen compound comprise at least one chiral centre, preferably one chiral centre.

50. A process according to any one of claims 44 to 49 wherein the sixth nitrogen compound and the seventh nitrogen compound are the same.

51. A process according to any one of claims 44 to 50 wherein the sixth nitrogen compound and/or the seventh nitrogen compound are/is an amino acid.

52. A process according to claim 51 wherein the amino acid is an acidic amino acid.

53. A process according to claim 52 wherein the amino acid is aspartic acid.

54. A process according to any one of claims 51 to 53 wherein the amino acid is L-amino acid.

55. A process according to claim 54 wherein the amino acid is L-aspartic acid.

56. A process substantially as described herein with reference to claim 1.

The Patent Office

27

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Claims searched: 1-56

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Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): C2C (CLT, CLU)

Int Cl (Ed.6): C07C 227/00 227/14 227/18

Other: Online: CAS ONLINE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
X	GB 1398277	(PETTERSON et al), see eg. page 4, lines 1-2	1 at least
X	GB 1098140	(DR. KARL THOMAE), see eg. Ex.5	1 at least
X	GB1081635	(HOFFMANN-LA ROCHE), see eg. Example	1 at least
X	GB1076146	(SINCLAIR), see eg. Ex.1	1 at least
X	GB1037375	(HOFFMANN-LA ROCHE), see eg. Exs.1 and 3	1 at least
X	GB 783887	(GEVAERT), see eg. Ex.1	1 at least

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